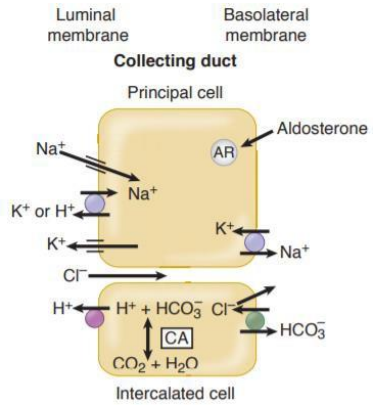
Potassium-Sparing Diuretics (low efficacy diuretics): Spironolactone, Eplerenone, Amiloride and Triamterene

Notes

- K^+-Sparing diuretics act on the distal portion of the distal tubule and the cortical collecting tubule: where Na^+ is exchanged for K^+ or H^+.



- The actions of the aldosterone antagonists depend on renal prostaglandin production; thus, their activity can be inhibited by **NSAIDs** under certain conditions (similar to loop diuretics and thiazides).

- They are two types:

1- Aldosterone antagonists: Spironolactone and Eplerenone.

- Aldosterone promotes reabsorption of Na^+ in exchange for K^+ (upregulates the Na+/K+ pump and sodium channels). net effect is ↑ Na^+ reabsorption, ↓ K+ reabsorption (↑ K^+, and H^+ excretion).

  ⇨ Aldosterone antagonists →↑ Na^+ excretion, ↓ K^+, and H^+ excretion.

- They are only effective in the presence of **aldosterone** (competitive antagonists).

- Given **orally**; have delayed onset of action requires several days.

- Weak diuretics, usually combined with other diuretics. They have great benefits in improving myocardial function in patients with heart failure.

- Spironolactone is an aldosterone antagonist with antiandrogenic activity (has side effects).

- Eplerenone is a spironolactone analog with much greater selectivity and potency for the aldosterone receptor. It is much **less active** on androgen and progesterone receptors than spironolactone and therefore has fewer adverse effects.

2- ENaC Blockers: Amiloride and triamterene.

- They are none steroidal potassium-sparing diuretics. They do not block aldosterone receptors, but instead directly interfere with Na^+ entry through the epithelial Na^+ channels (ENaC) in the apical membrane of the collecting tubule.

- Triamterene is metabolized in the liver, but renal excretion is a major route of elimination for the active form. It has a shorter half-life and must be given more frequently than amiloride (not metabolized).

Indications

- Spironolactone is particularly useful in **hyperaldosteronism states**, i.e. in the treatment of resistant hypertension due to primary hyperaldosteronism and of refractory edema associated with secondary aldosteronism (cardiac failure, hepatic cirrhosis, nephrotic syndrome, and severe ascites).
- **Hypokalemia**; since they decrease K^+ excretion.
- **Hirsutism** (antiandrogenic effect of aldosterone antagonists).
- They are available alone or combined with thiazides: thiazide-induced hypokalemia and metabolic alkalosis are ameliorated.

Toxicity

- **Hyperkalemia:** can cause mild, moderate, or even life-threatening hyperkalemia → cardiac arrhythmias. It is more severe with **eplerenone** and more common in patients with diabetes, chronic renal disease or patients on ACE inhibitors
- **Hyperchloremic Metabolic Acidosis:** by inhibiting H^+ secretion in parallel with K^+ secretion, the K^+-sparing diuretics can cause acidosis.
- **Gynecomastia:** Spironolactone may cause Gynecomastia, impotence, benign prostatic hyperplasia in males and breast tenderness in females (rare with Eplerenone as they are side effects due to the antiandrogenic activity).
- **Acute Renal Failure**: the combination of triamterene with indomethacin (NSAID) may cause acute renal failure. This has not been reported with other K^+-sparing diuretics.
- **Kidney Stones:** Triamterene is only slightly soluble and may precipitate in the urine, causing kidney stones.
- **Contraindications:**

  a- Oral K^+ administration should be discontinued if K^+-sparing diuretics are administered.

  b- Concomitant use of other agents that blunt the renin-angiotensin system (β blockers or ACE inhibitors) increases the likelihood of hyperkalemia.

  c- Patients with liver disease may have impaired metabolism of triamterene and spironolactone, so dosing must be carefully adjusted.

  d- Strong CYP3A4 inhibitors (e.g., ketoconazole) can markedly increase blood levels of eplerenone.

Agents that alter water excretion: 1- Osmotic Diuretics and 2- ADH

1- Osmotic diuretics: Mannitol, urea, and glycerol			
Notes	**Pharmacology**	**Indications**	**Toxicity**
- The **proximal tubule** and descending limb of Henle's loop are freely permeable to water. Any osmotically active agent that is filtered by the glomerulus but not reabsorbed promotes a water diuresis due to **increased** tubular osmolarity. ⇨ Osmotic diuretics have their major effect in the proximal tubule and the descending limb of Henle's loop; where water is freely reabsorbed mostly. - Mannitol is a **sugar**, not absorbed by kidney tubules, has no systemic effects and not metabolized.	- Mannitol is not absorbed by the GI tract; thus, it must be given **parenterally**. - Mannitol is not metabolized and is excreted by glomerular filtration within 30–60 minutes, without any important tubular reabsorption or secretion. - Through osmotic effects, they also oppose the action of ADH in the collecting tubule. As a result, **urine volume increases**. The increase in urine flow rate **decreases** the contact time between fluid and the tubular epithelium, thus reducing Na^+ as well as water reabsorption. - The resulting natriuresis is of **lesser** magnitude than the water diuresis, leading eventually to excessive **water loss and hypernatremia**.	- **Increase of Urine Volume:** used to maintain urine volume and to prevent anuria/oliguria states due to large pigment loads to the kidney (rhabdomyolysis) [(1)]. - **Reduction of Intracranial** and **Intraocular Pressure Osmotic:** diuretics are used to reduce intracranial pressure, cerebral edema and brain mass before and after neurosurgery, and to reduce intraocular pressure in glaucoma before ophthalmologic procedures. ⇨ The above therapeutic uses are based on the fact that osmotic diuretics increase the osmotic pressure of plasma thus extract water from the eye and brain.	- **Extracellular Volume Expansion:** Mannitol extracts water from cells before reaching the kidney and causing diuresis. This leads to the expansion of extracellular volume and hyponatremia. - **Hyponatremia**: in patients with **diminished** renal function, mannitol is retained intravenously and causes osmotic extraction of water from cells, leading to hyponatremia. - **Dehydration, Hyperkalemia, and Hypernatremia**: as water is extracted from cells, intracellular K^+ concentration rises, leading to hyperkalemia. - Headache, nausea, and vomiting.

1- Pigment nephropathy is an abrupt decline in renal function as a consequence of the toxic action of endogenous heme-containing pigment on the kidney tubules. Such pigments include myoglobin, released from skeletal muscle in rhabdomyolysis, and hemoglobin, released during intravascular hemolysis.

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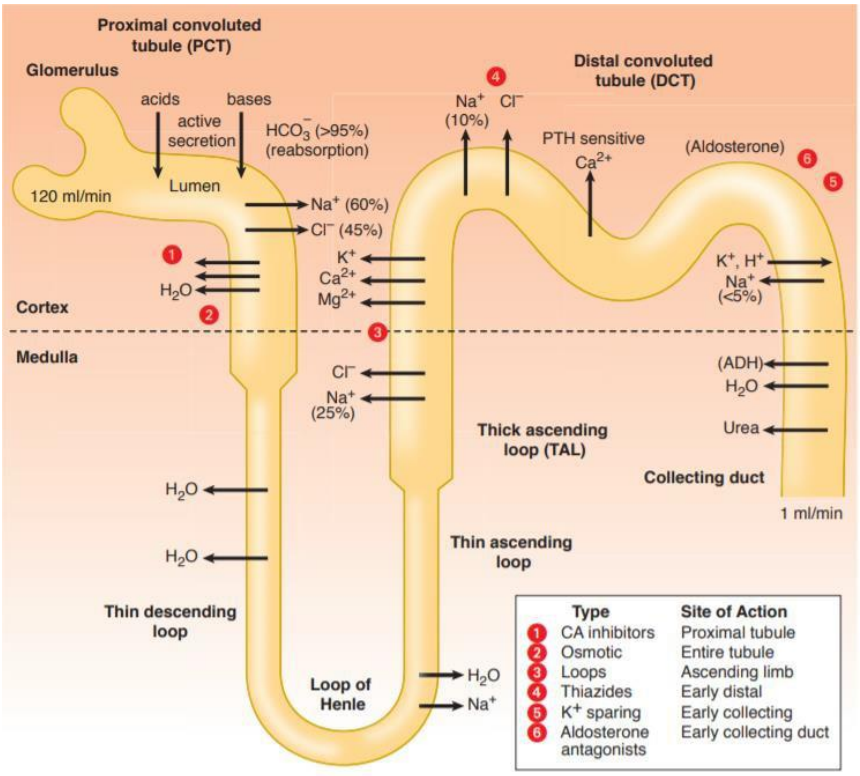
2- ADH: Vasopressin and desmopressin			
Notes	**Pharmacology**	**Indications**	**Toxicity**
- They are used in the treatment of **central diabetes insipidus**. - Their renal action is mediated primarily via **V_2** receptors ➔ ADH stimulates water reabsorption through stimulating insertion of "water channels" or **aquaporins** into the membranes of kidney tubules. These channels transport solute-free water through tubular cells and back into the blood, leading to a decrease in plasma osmolarity and an **increased osmolarity of urine**.	- Antidiuretic hormone **antagonists** inhibit the effects of ADH in the collecting tubule. - **Conivaptan** is a pharmacologic antagonist at V_{1a} and V_2 receptors. It is only available for **IV** use. - Other **nonselective** agents are **Lithium** and **Demeclocycline** (a tetracycline antimicrobial drug that has anti-ADH effects). Both lithium and demeclocycline reduce the formation of cAMP in response to ADH. - Conivaptan and demeclocycline have half-lives of 5–10 hrs.	- **Syndrome of Inappropriate ADH Secretion** (excessive insuppressible release of ADH)**:** ⇨ **Lithium carbonate** is used to treat this syndrome, but the response is unpredictable. ⇨ **Demeclocycline** yields a more predictable result and is less toxic. ⇨ **Conivaptan** is administered by IV injection, so it is not suitable for chronic use in outpatients. ⇨ **Water restriction** is often the treatment of choice. - ADH is also elevated in response to diminished effective circulating blood volume, as often occurs in **congestive heart failure**. when treatment by volume replacement is not desirable, dangerous hyponatremia may result. ⇨ **Conivaptan** may be particularly useful because blockade of V_{1a} receptors by this drug leads to decreased peripheral vascular resistance and increased cardiac output.	- **Nephrogenic Diabetes Insipidus:** ADH antagonists can cause severe **hypernatremia** and **nephrogenic diabetes insipidus** (a disorder caused by complete or partial resistance of the kidneys to vasopressin). Nephrogenic diabetes insipidus can be treated with a **thiazide diuretic**. - **Renal Failure:** both lithium and demeclocycline have been reported to cause acute renal failure. Long-term lithium therapy may also cause chronic interstitial nephritis. - **Demeclocycline** should be avoided in **liver disease** and children younger than 12 years.

Diuretic Combinations	
Loop Agents + Thiazides	**K^+-Sparing Diuretics + Loop Agents or Thiazides**
- The combination of loop diuretics and thiazides can mobilize large amounts of fluid, even in patients who have not responded to single agents. Salt reabsorption in either the TAL or the DCT can increase when the other is blocked. Inhibition of both produces **more** than an additive diuretic response. - K^+-wasting is extremely common and may require **parenteral** potassium administration with careful monitoring of fluid and electrolyte status.	- **Hypokalemia** develops in many patients taking loop diuretics or thiazides. This can usually be managed by taking dietary KCl **supplements**. - When hypokalemia cannot be managed through supplements, the addition of a K^+-sparing diuretic can significantly lower K^+ excretion. - It should be **avoided** in patients with **renal insufficiency** and in those receiving **ACE inhibitors**, in whom life-threatening **hyperkalemia** can develop in response to K^+-sparing diuretics.

Useful Notes



Drug	Mechanisms of Action	Urinary Electrolytes	Blood pH
Acetazolamide	Inhibition of carbonic anhydrase in PCT	↑ Na^+ ↑ K^+ ↑↑ HCO_3^-	Acidosis
Ethacrynic acid, furosemide, torsemide	Inhibition of $Na^+/K^+/2Cl^-$ cotransporter in TAL	↑↑ Na^+ ↑ K^+ ↑ Ca^{2+} ↑ Mg^{2+} ↑ Cl^-	Alkalosis
Hydrochlorothiazide, indapamide, chlorthalidone	Inhibition of Na^+/Cl^- cotransporter in DCT	↑ Na^+ ↑ K^+ ↑ Cl^- ↓ Ca^{2+}	Alkalosis
Amiloride, triamterene, spironolactone, eplerenone	Block Na^+ channels, block aldosterone receptors in collecting tubule	↑ Na^+ (small) ↓ K^+	Acidosis

- ⇨ All diuretics increase Na^+ excretion.
- ⇨ HCO_3- in urine ➔ CAIs
- ⇨ ↑ Ca^{+2} in urine ➔ Loop diuretics
- ⇨ ↑ Ca^{+2} in urine ➔ Thiazides

- Mannitol is contraindicated in CHF and pulmonary edema because it draws water from the cells and increases the filling pressures of the heart.
- Combining K^+-sparing diuretics with ACEIs or ARBs may cause **hyperkalemia** (contraindicated).
- **Eplerenone** is a selective aldosterone receptor blocker devoid of antiandrogenic effect.
- An important difference between loops and thiazides is that loops promote calcium excretion, while thiazides decrease calcium excretion.
- Allergies to Sulfonamide containing drugs, cross-allergenicity with:
  - **a-** Carbonic anhydrase inhibitors
  - **b-** All loop diuretics, except ethacrynic acid
  - **c-** Thiazides
  - **d-** Sulfa antibiotics
- Diuretic of choice for **acute pulmonary edema** are loop diuretics, if the patient has **sulfonamide allergies**, then the drug of choice is ethacrynic acid.
- Thiazides are the diuretics of choice for hypertensive patients. They also treat nephrogenic diabetes insipidus.
- **Oliguria states** ➔ Mannitol
- **High ceiling diuretics (most efficacious) / in acute renal failure** ➔ Loop diuretics
- **NSAIDs inhibit their actions** ➔ Thiazides, Loop, and K^+ sparing diuretics.
- **Hyperuricemia** ➔ Thiazides and Loop diuretics.

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